***Review Article***

# EFFECTS OF OCCUPATIONAL EXPOSURE OF SELECTIVE CHEMICALS ON DIABETES MELLITUS: A REVIEW


## ABSTRACT

Diabetes mellitus is a disease caused by the disorder in carbohydrate metabolism and it is characterized by impairment in insulin production by the body cells. Beta cells located within clusters of cells in the pancreas are responsible for the secretion of insulin whose role in the body is to stimulate cells to take up and metabolize glucose. Dysfunction of beta cells re usually found in people with diabetes mellitus and this results in reduced glucose uptake/metabolism by the cells. Thiswork centers on a comprehensive review of possible relationships between occupational exposure to specific chemical substances or industrial activities and diabetes mellitus-related outcomes, including alterations in glucose homeostasis and diabetes mellitus incidence/prevalence or mortality.Many occupational chemicals have been seen to have adverse effects on diabetes mellitus. Such chemicals include metals like cadmium and arsenic, hydrocarbons like benzene, methane and organophosphates. Studies revealed that different concentrations of heavy metals increase the risk of diabetes mellitus. Exposure to toxic metals like cadmium due to uncontrolled pollution and industrialization increases defect in glucose uptake and other problems. Study on occupational chemical exposure disclosed that exposure to 0.84-mg/kg of cadmium in model organisms accelerated the concentration of blood glucose. Study also revealed that exposure of diabetic mice to volatile benzene-increases insulin resistance in the liver and skeletal muscle. Exposure to perfluorinated alkyl substances (PFAS) which are used in fire-fighting foam, textiles, kitchen ware, and food packaging material have been shown to be associated with diabetes in an elderly population, backing the view that perfluorinated alkyl substances can alter glucose metabolism in humans and induce Type 2 diabetes mellitus. Moreso, in this review, the complications associated with diabetics exposed to industrial chemicals is discussed and management highlighted.



Keywords: Diabetes mellitus, glucose homeostasis, cadmium in model organisms, secretion of insulin


## INTRODUCTION

Diabetes mellitus is a disease caused by the disorder in carbohydrate metabolism and it is characterized by impairment in insulin production by the body cells (Kara,2017). Beta cells located within clusters of cells in the pancreas are responsible for the secretion of insulin whose role in the body is to stimulate cells to take up and metabolize glucose.Dysfunction of beta cells

re usually found in people with diabetes mellitus and this results in reduced glucose uptake/metabolism by the cells( Kara,2017).

Retinopathy, nephropathy and neuropathy, among other complications are some of the long-term complications of diabetes mellitusand also people with this disease have high tendency of suffering from other disease conditions like obesity, heart disease, peripheral arterial and cerebrovascular disease, erectile dysfunction, and fatty liver disease(WHO,2019). Thirst, polyuria, blurring of vision, and weight loss are some of the characteristic symptoms of diabetes.

Research carried out revealed that about 13.6million people in African continent counts have diabetes and also Sub-saharanAfrica which is the African Region of IDF have about 7 million people living with diabetes (Sylvester *et al*., 2015). The number of people living with diabetes in this African is predicted to increase by 2025 and may reach 15 million.

The pathophysiology of this disease isnot well understood, although the disease epidemiology and inheritance patternshows that the disorder originatefrom genetic and lifestyle risk factors, such intake of excessive calories,excessive weight and obesity, love as well as cigarette smoking (Hu, 2011). Most epidemiological studies have linked diabetes mellitus to environmental contaminants (Carpenter, 2008; Hectors *et al.*, 2011; Howard *et al*., 2011;Kuo *et al.*, 2013; Longnecker and Daniels,). Information on how occupational chemicals affect the pathogenesis and clinical history of the diabetes mellitus is still lacking. A number of studies has been carried out to know whether heavy metals such as Chromium (Cr), Arsenic (As), lead (Pb), Iron (Fe) and Nickel (Ni) could be involved in diabetes related outcome in industries where these metals are being used.

Therefore, the present review aims to give a comprehensive review of the possible relationship between occupational exposure to specific chemical substances or industrial activities and diabetes mellitus-related outcomes, including alterations in glucose homeostasis, diabetes mellitus incidence/prevalence or mortality, with a specific focus on the biological plausibility, dose–response relationship and temporality.

**Epidemiology and Global Burden of Diabetes**

Diabetes is a global disease, occurring in both rural parts of low and middle countries. The number of people with diabetes worldwide was estimated to about 422 million adults as at 2014 (WHO,2019).

About 1.1 million children and adolescents aged 14-19 years were estimated to have type 1 diabetes mellitus by the International Diabetes Federation.Study performed by the IDF in 2017, prove that without proper action taken to reduce the diabetes increase, there will be at least 629 million people living with diabetes by 2045(IDF,2017). Studies shows that about 4 million death year is caused by hyperglycemia in and the international Diabetes Federation estimates that the yearly global health care spending on diabetes among adults was US$850 billion in 2017(IDF,2017).

**Aetiology of Diabetes**

Beta cells dysfunction or destruction is main cause of diabetes mellitus(Figure 1). A decline in the function or the complete destruction of B-cells can also be caused by other underlying factors (Perl *et al*., 2010). Genetic predisposition and abnormalities, epigenetics processes, insulin

resistance, auto-immunity, concurrent illnesses and inflammation are some of the underlying factors that can cause beta cells dysfunction.

.Diabetes aetiology differs no depending on the genetic makeup, family history, ethnicity, health and environmental factors.

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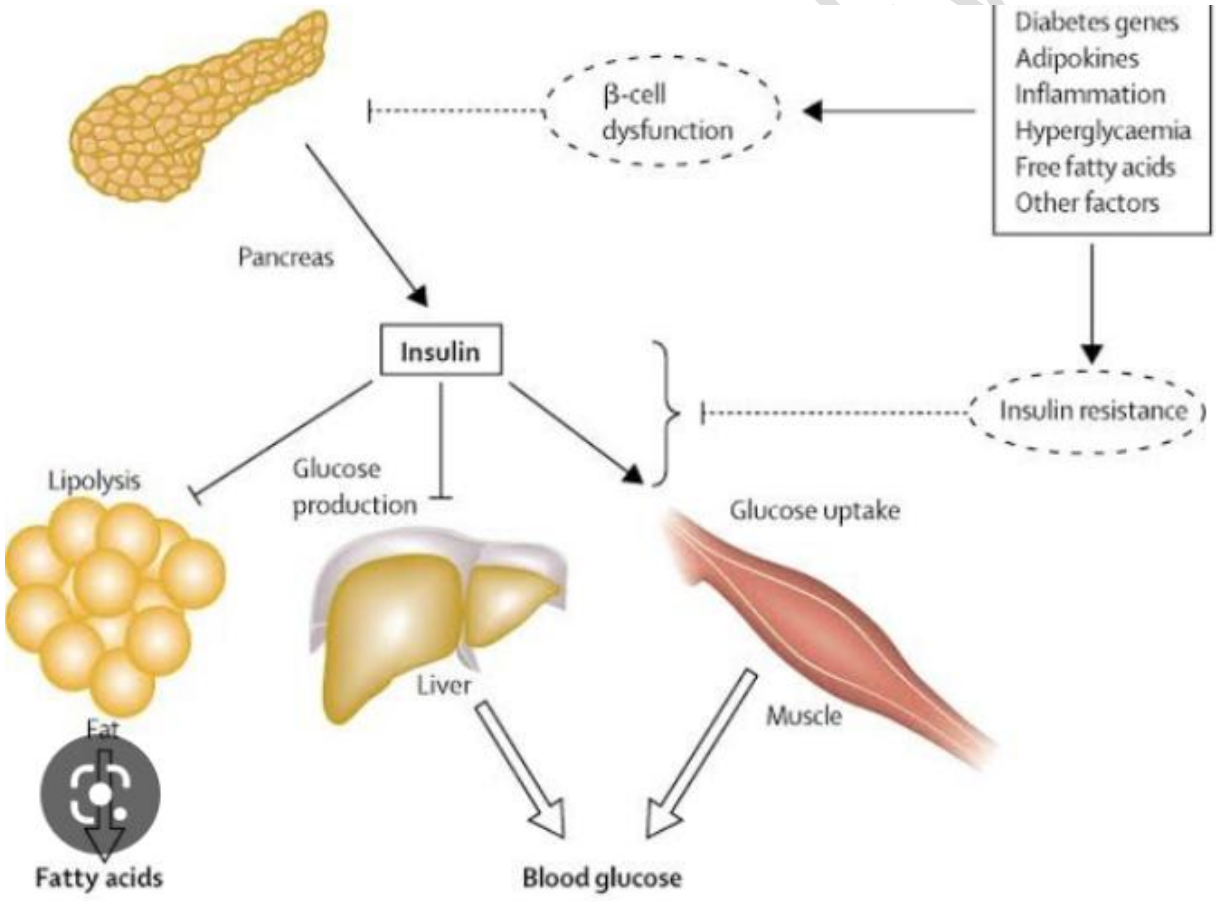


Figure 1.: Diagram showing the causes of Diabetes mellitus
Source:Kara,,(2017)

## CLASSIFICATION OF DIABETES MELLITUS

Classification system helps health care professionals choose appropriate treatments are choosed by experts (WHO, 2019).

. According to WHO Classification, the types of diabetes mellitus include:

**Type 1 Diabetes:** There are no data available on Type 1 diabetes mellitus trends, globally but there is an increase in the incidence of type 1 diabetes mellitus in childhood between 3% and 4%, annually, in high-income countries (Patterson *et al.,* 2009). Type 1 diabetes mellitus affect both males and females. Type 1 diabetes mellitus prognosis is difficult in countries with limited access to insulin (WHO, 2019). T1DM symptoms occur rapidly in children, although it may also occur in adults. Ketoacidosis is usually presented as the first sign of manifestation of this disease , especially in children and adolescents(Jackson *et al.*, 2001).

Moderate hyperglycemia which can change rapidly to severe hyperglycemia and/or Ketoacidosis in the presence of infection or other stress may be seen in other patients (WHO,2019).Immune-mediated process with beta cell autoantibodies against glutamic acid decarboxylase, islet antigen-2 , ZnT8 transporter or insulin, and associations with genes controlling immune responses have been seen in 70% - 90% of people with type 1 diabetes mellitusat diagnosis(EiSenbarth*et al.,* 2007). The specific pathogenesis in those without immune features is unclear although some may have monogenic forms of diabetes.

Type 1 diabetes symptoms can appear suddenly and may include thirstiness, frequent urination, blurred vision, weight loss, fatigue, hunger and bed-wetting in children.

**Type 2 Diabetes Mellitus:** About 90% - 95% of diabetes affecting humans is the type 2 diabetes mellitus,being highin low and middle Income countries(WHO ,2019). Type 2 diabetes is a serious world health problem,arising in relation to cultural, economic, social and dietary changes such as highly processed foods and sugar– sweetened beverages, consumption increase , reduced physical activity, obesity, unhealthy lifestyle patterns, fetal malnutrition, and hyperglycemiaexposure during pregnancy(WHO,2019). Adults are more susceptible to T2DM, althoughgreater number of children and adolescents are also affected (WHO,2016).

Insulin is seen in most people with this disease and in the onset of this disease, there is increase in absolute insulin levels with resistance to the action of insulin (Kahn *et al.*,2014). Obesity/ overweight is common among people with T2DM and this either causes or increase insulin resistance (Stumvol*et al.*, 2005). Treatment with insulin is not required in people with type 2 diabetes, althoughit may be required to lower blood glucose to avert chronic complications.

Age, obesity, unhealthy lifestyles and prior gestational diabetes are some factors that can increase of developing type 2 diabetes mellitus. The frequency of T2DM also varies between different racial and ethnic subgroups, especially in young and middle-aged people ( WHO,2019). Some symptoms of T2DM include blurred vision, fatigue, thirstiness, numbness in the hands and feet, slow healing of cuts or sores and weight loss.

**Hybrid Forms of Diabetes:** Proposal of new categories of diseases is due to efforts made indifferentiating T1DM from T2DM , and this hybrid form of diabetes are the slowly evolving immune-mediated diabetes and ketosis prone T2DM (Atkinson *et al.*, 2014)

**Slowly Evolving Immune-Mediated Diabetes**: This hybrid form of diabetes is common in adults,having pancreatic autoantibodies that can react with non-specific cytoplasmic antigens in islet cells, Glutamic acid decarboxylase, protein tyrosine phosphatase A-2, insulin, or ZnT8 (WHO,2019). The latent autoimmune diabetes in adults was it's common name (WHO,2019). Insulin therapy is not needed in people with this type of diabetes at diagnosis. Lifestyle modification and oral was an initial way of controlling this type of diabetes but now progress to use of insulin more rapidly than people with typical T2DM (Sobngwi*et al.*, 2002). The symptoms of this type diabetes is similar to other form: polydipsia (excessive thirst), polyuria and often blurred vision.

**Ketosis-prone Type 2 :** A young African-American was the first to identify this hybrid form of diabetes (Winter *et al.*, 1987) and it has become a new clinical entity (Mauvais*et al.*,2004). This type of diabetes has diversely been delineated has a form of T1DM or T2DM (WHO, 2019). Some advocate that people classified with idiopathic or type 1 B diabetes of T1DM or T2DM Should be reclassified as having ketosis-prone type 2 diabetes (Sobngwi*et al*., 2002). Specific epidemiologic, Clinical, and metabolic features of diabetes onset and natural history of impairment in insulin secretion and action can be used to differentiate ketosis-prone T2DM from T1DM and classical T2DM (WHO,2019).

**Other Specific forms of Diabetes**

**Monogenic Diabetes:** Molecular genetics has been defined by WHO so that they can help identify specific subtypes of diabetes. Subgroups that are genetically have been disclosed through this advances,resulting in new genetics identification (WHO, 2019). Genetic diagnosis

which is an outstanding advance can result in improved treatment outcomes for some people (WHO,2019)Classification of monogenic subtypes of diabetes is based on the uses of gene symbol of the mutated gene followed by the clinical syndrome (Hatterseyet *al.*, 2009). For example, a child diagnosed with neonatal diabetes (PNDM) due to a mutation in KCNJ11 is labeled as having KCNJ11 PNDM. If there is a clinical diagnosis of PNDM but a gene mutation had neither been looked for nor found, then the person would be categorized as PNDM only( WHO,2019).

**Monogenic Defects of β-cell Function:**Maturity-onset diabetes of the young (MODY), permanent neonatal diabetes (PNDM), transient neonatal diabetes (TNDM) and genetic syndrome are clinical indications of monogenic defects in beta cell function, linking insulin-deficient diabeteswith specific clinical characteristics (Hattersley et al., 2006). MODY which is an inherited early-onset familial diabetes that is not dependent on insulin and results from β-cell dysfunction was clinically discovered(Tattersall.,1978).

Mutations in the gluco-kinase gene result in the commonest genetic subtypes and hepato-nucear factor gene (HNF1A MODY and HNF4A MODY) (Shields *et al.*, 2010).Glucose-kinase gene MODY results in life-long mild fasting hyperglycemia that deteriorates with age.Micro-vascular complications are rarely developed by these people and pharmacological treatment for hyperglycemiaare not required(Hattersley*et al.*, 2010).

Progressive and marked hyperglycemia with a high risk ofmicrovascular and macrovascularcomplications is the hallmark of HNF1A MODY (WHO,2019). People with this subtype are sensitive to the hypoglycemic effects of sulfonylureas (Hattersley*et al.*, 2010), allowing people with insulin-treated HNF1A to be successfully transferred to sulphonylureas (Hattersley*et al.*,2006).

**Monogenic Defects of Insulin Action :** Monogenic causes of insulin resistance are not common when compared to monogenic β-cell defects (WHO, 2019). They are typically present with characteristic features of insulin resistance in the absence of obesity, including hyperinsulinemia, acanthosisnigricans, polycystic ovarian disease and Jul (Kahn *et al.*, 1976). Diabetes starts when the β-cells fails to equilibrate for the insulin resistance (WHO, 2019).

Mutations in the insulin receptor give rise to several clinical manifestations and degrees of hyperglycemia (Taylor *et al*, 1992). The two pediatric syndrome that have mutations in the insulin receptor gene with extreme insulin resistance, dymorphism, severe intrauterine and mortality (Taylor *et al*., 1999). Insulin resistance is a feature associated with lipid storage disorders and it is characterized by lipodystrophy (Taylor*et al*.,1999). Familial partial lipodystrophy is a persistent condition characterized by limb lipoatrophy in young adult life, associated with hyperlipidemia and insulin resistant diabetes **(**WHO,2019). Mutations in the LMNA gene coding for nuclear Amin A/C are the commonest risk factor (Owen *et al*., 2007). PPARG mutations also result in a partial lipodystrophywhich is usually associated with severe insulin resistance, early onset T2DM and hypertension (Barroso*et al.*, 1999).

**Diseases of the Exocrine Pancreas:** Diseases which damage the pancreas can cause diabetes (WHO,2019). Pancreatitis, trauma, infection, pancreatic cancer and pancreatectomyare some of these (Ewad*etal*.,2012).Pancreatic damage must be severe for diabetes to occur**.** Adenocarcinomas involvinglittle portion of the pancreas have been linked with diabetes (WHO, 2019). This involve mechanism other than simple reduction in β-cell mass (Permert*et al.*,1994). Both exocrine pancreatic failure and reduced insulin secretion are seen in cystic fibrosis,

resulting in diabetes, although the relationship between these two defects is not clear (Dobson*et al.*,2004).

**Endocrine Disorders:** Many hormones like growth hormone, cortisol, glucagon, epinephrine are capable of disrupting the action of insulin. Diseases such as acromegaly, Cushing's syndromeglucagonoma and pheochromocytomawhich occur due to excessive secretion of these hormones can cause diabetes (MacFarlane *et al.*, 1997). Hyperglycemia occuring due to this conditions be corrected when the condition causing excessive increase/raise in the hormone is treated successfully (WHO,2019).

**Drug or Chemical-Induced Diabetes:** Corticosteroids, Beta-blockers, Thiazide diuretics, Antipsychotics, Statin, Pyrinuron, Pentamidine, Interferon-Alpha, Nicotinic acid and Dilantin are some drugs that can affect insulin secretion/action(WHO,2019). Due to insulin resistance or β-cell dysfunction in people, this drug can cause diabetes (Pandit*et al*., 1993). Pyrinuron (a rat poison) and pentamidine are some toxins which can destroy pancreatic β-cells permanently (Esposti *et al*.,1996).

**Infection-related Diabetes:** Destruction of β-cell have been linked with virus, causing Type1 Diabetes Mellitus (T1DM), but their manner of causes remained uncertain (WHO, 2019). People with congenital rubella also have diabetes (Forrest *et al*, 1971). Type 1 diabetes mellitus have

been seen to be induced by Coxsackie B and viruses such as cytomegaovirus, Adenovirus and mumps(King *et al.*,1983).

**Uncommon Specific Forms of Immune-Mediated Diabetes**: Specific immune diseases are linked with diabetes and they have distinct causes to those that lead to T1DM (WHO, 2019). Symptoms of hypoglycemia are usually seen in people immune mediated diabetes.An autoimmune disorder of the central nervous system, the stiff man syndrome is characterized by axial muscles stiffnesswith painful spasms (Hirata *et al* ,1972). High titres of Glutamic acid decarboxylase (GAD65) autoantibodiesare found in people with this form of diabetes and about half will develop diabetes (WHO,2019). It has been reported that people who received interfon-alpha can develop diabetes which is linked with islet cell autoantibodies and, in some cases, severe deficiency of insulin (Fabris*et al.*,1998).

Receptor of insulin autoantibodies have ability to initiate diabetes by binding to the receptor, thereby decreasing the binding of insulin to target tissues (Kahn *et al*.,1997). Hypoglycemia can also occur when the insulin receptor autoantibodies act as an insulin agonist after binding to the receptor (WHO,2019). Patents with systemic lupus, erythematosus and other autoimmune diseases may also have insulin receptor autoantibodies (Rosenste*et al.*, 2001). Acanthosisnegricans are usually found in people with insulin receptor autoantibodies these type of syndrome is termed type B insulin resistance.

## SYMPTOMS AND HEALTH CONSQUENCES OF DIABETES

According to WHO, some general symptoms of diabetes mellitus include:

- Frequent urination
- Thirstiness
- Loss of weight
- Hunger
- Blurred vision
- Numbness or tingling of hands or
- Feet damage
- Skin damage
- Delayed wound or sore healing
- Infections

**HEALTH CONSEQUENCES OF DIABETES**

- **Cardiovascular disease:**This is the commonest and leading cause of diabetes, globally. Damage to blood vessels and the nerves that control the heart. Can occur due to high blood sugar (CDC,2014). A two to three fold increased risk of heart attacks and strokes are seen in adults with diabetes(WHO,2019). Cardiovascular problems, such as coronary artery disease with chest pain (angina), heart attack, stroke and narrowing of arteries (atherosclerosis) are also seen in diabetic patients.
- **Nervous damage (neuropathy):** Excess sugar can damage capillariesthat nurture the nerves, especially in the leg,resulting in tingling, numbness, burning or altered pain sensation( Mayor,2021). A person can lose all sense of feeling in the affected limbs, if not treated. Nausea, vomiting, diarrhea or constipation (Diabetesketoacidosis) can occur due to damage of nerves associated with digestion.Erectile dysfunction in men can also occur due to neuropathy (Mayor,2021).

- **Kidney damage (nephropathy):** Damage to the tiny blood vessels in the kidney can result in diabetes and kidney failure or kidney disease can occur due to strong damage (Mayo, 2021). Tissue scarring, urine protein loss and severe kidney disease which can require dialysis or kidney transplant can occur due to nephropathy(Hossam, 2015).

- **Retinopathy:**Damage to blood vessels in the retina of the eye (diabetic retinopathy) can occur due to diabetes,resulting in vision loss. Other serious vision conditions, such as cataracts and glaucoma can also occur (Mayo, 2021).

- **Foot damage and Skin conditions:** The risk of various foot complications can be increased due to damage of nerves in the feet or poor blood flow to the feet, resulting in cuts and blisters development with serious infections, if not treated. (Mayo,2021). Also the skin can be prone to diseases such as bacterial and fungal infections due to diabetes. Some skin rashes is usually found in the skin of a person suffering diabetes and this rashes are collectively known as diabetic dermadromes (Hossam,2015).

- **Alzheimer's disease:** Alzheimer's disease is a brain disorder, characterized by brain changes, resulting deposition ofcertainproteins. (Mayor,2021). The risk of dementia, such as Alzheimer's disease may increase due to type 2 diabetes.


Figure 2: Diagram showing the health Consequences of diabetes mellitus.
Source: Hossam,(2015).

**SOME OCCUPATIONAL CHEMICALS AND DIABETES MELLITUS**

Occupational or industrial chemicals are chemicals use in industries for production purposes. Exposure to most of these chemicals is seen to have some health impact. Some of the occupational chemicals which may have effects on diabetes include metallic compounds, hydrocarbons compounds and other compounds.

**Diabetes Mellitus and Metallic Compounds:**Naturally, heavy metals are existing metallic elements whose atomic weights and densities are high (Ferguson *et al*.,1990). Over a hundred

milligrams of a macro metals such magnesium are required in our everyday diet while less than 100 ppm of macronutrients like manganese, cop-per, nickel, zinc, and iron are required.(Soetan*et al* ,2010). These metals are important in several physiological and biochemical processes in the body (Fraga, 2005). Most studies suggest that uncertainty in the quantity of these metals results in significant side effects on health like that of pancreatic islets, which lead to the occurrence of diabetes. (Planchart et al., 2018). Heavy metals like cadmium, (Ni), mercury, arsenic, and lead exert toxic effects on human health. These metals have been seen to affect patient with Type 2 Diabetes Mellitus, impairing glucose uptake and glucose regulation (Khan *et al*., 2014).

In many studies, the length to which heavy metals affect diabetic patients have been measured. (Anam*et al*.,2021). The results reveal that a different concentration of heavy metals increases the risk of diabetes mellitus (Planchart*et al.*, 2018). Exposure to toxic metals like Pb, Ni, Cd, and Hg due to uncontrolled pollution and industrialization increases defect in glucose uptake disturbance and other problems (Anam*etal*.,2021).

**Cadmium:** Cadmium is one of the heavy metals which is soft and silver-white, being very toxic. (Anam*et al.*,2021). Naturally, cadmium is present in air, water, and soil and overly distributed in the earth's crust. Industrially, it is used in alloy, pigments, and batteries production. Because of its toxicity, it is not commonly used in developed countries. (Anam*et al*., 2021). In an experiment carried out, it was seen that exposure to 0.84-mg/kg of Cd in model organisms remarkably accelerated the concentration of blood glucose (Bell *et al*., 2003). Remarkable escalation in glucose and serum concentration decrease in experimental animals as compared to control animals after exposure was observed (Lei *et al*.,2008).

Moreover, the precise mechanism of action and effect of cadmium on secretion, production, utilization of Insulin and blood glucose regulation is not known because only view reports have

been made on the link of cadmium and diabetes until now (Chen *et al.*,2009). Many studies carried out recognized cadmium's contribution in glucose trans-porter-4 (GLUT4) down regulation and the increased alteration of pancreatic beta cells in diabetes (Chen *et al*., 2009). Diabetes associated with exposure to cadmium was seen in rat adipocytes (Anam*et al.*, 2021).There was an observation in Decreased GLUT4 protein and mRNA expression was also observed as well as lowglucose tolerance in experimental rats (Han *et al.*, 2003). Accumulation of Cadmium metal causes several dysfunctions like cell degeneration or necrosis and weak degranulation in pancreatic β cells as shown by many experimental studies.

**Arsenic:** Arsenic (As, )a chemical elementoccurring naturally and distributed widely in the earth's crust (NIH, 2016). It's level in the environment differs, found commonly in water, air and soil. Organic arsenicwhich contain carbon and inorganic arsenic which is highly toxic are the two types of arsenic. (NIH, 2016).Smelters and glass workers used arsenic during production andit is used in production of arsenic containing pesticides (Beard *et al.,* 2003). The link between Arsenic exposure and different diabetes mellitus outcome have been investigated by most research studies (Bartoli *et al*., 1998). Drinking water from private wells can be contaminated by arsenic especially throughout South East-Asia and Latin-America (Danglebe*et al*., 2013). There are no epidemiological studies investigating associations between arsenic exposure and T1DM development. Immune system in humans and animal models were seen to be impaired due to exposure to arsenic (Danglebe*et al.*,2013), alteration of gut microbiomediversity, metabolic profiles of microbiomes well as inhibition of glucose stimulated insulin release in mice were also observed (Douille*et al.*, 2013).

**Diabetes Mellitus and Hydrocarbons:** Organic molecules that consist mainly carbon and hydrogen atoms are termed Hydrocarbons. Hydrocarbons can be aromatic or aliphatic. Hydrocarbons with closed ring structures are called aromatic hydrocarbons while those with linear chain structures are called aliphatic hydrocarbons(Silderberg, 2004). Both types of hydrocarbons canundergo modification by replacing the hydrogen atoms with halogens, thereby changing their physical and chemical properties (Leso*et al*., 2017). Hydrocarbons found in industries are used mainly as solvents, raw material in plastics/rubber production, as fire extinguisher , metal cleaning agents, fumigants and Insecticides (ILO, 2015).

**Diabetes Mellitus and Aromatic CompoundsAromatic:** Hydrocarbons are Hydrocarbons with a closed ring structure. Examples of aromatic hydrocarbons are Benzene, Napthalene, Phenanthrene, Methylbenzene, Trinitrotoluene and O-dihydroxybenzene.

**Benzene:** It is the commonest complex aromatic hydrocarbon. The bonding nature of Benzene was first discovered by August Kekulé in the 19thcentury. Benzene is an organic hydrocarbon which is colourless and has a molecular structure $C_6H_6$ (figure 4). Benzene is mainly used as solvent in industries and it is widely used in production of various polymers, resins and synthetic fibers (Bahadar*et al.,* 2014). Studieshave been carried out to investigate the mortality rate of diabetes mellitus in relation to benzene exposure during the production, processing, recovering, loading and unloading of benzene contained materials (Bond et al.,1986). Disturbance of glucose homeostasis and glucoseintolerance is seen in experimental models exposed to benzene.

Study revealed that exposure of diabetic mice to volatile benzene-increases insulin resistance in the liver and skeletal muscle. This is due to Nuclear factor Kappa (Nf-kb) activation, Macrophage inflammatory protein (Mip-1α) expression, and Suppressor of cytokine signaling 1-

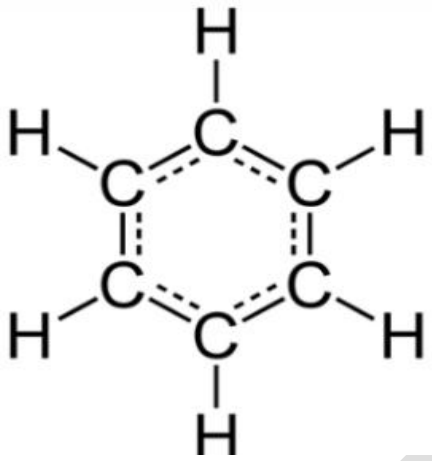

Figure 3.: Structure of Benzene
Source: Bahadar*et al.*,(2014)

mediated inhibition of Akt-phosphorylation, thereby inhibiting insulin receptor substrate(Ir-2)phosphorylation (Wesley *et al.*,2019).

**Methane:** Methane is a colourless and odourless gas which exists in nature abundantly, and it is a produced as a result of activities carried out by humans. The simplest member of the paraffin sequence of hydrocarbons is methane and is seen to be one of the most potent of the greenhouse gases with a chemical formula is $CH_4$( figure 4). Methane is water soluble, burning at ease in air to form $CO_2$ and water vapour. Methane is produced naturally by an anaerobicdecomposition of vegetable matter under water by bacteria. Methane is a the major constituent of natural gas and also exist as the component of flammable gas together with coal steam.(Britannica,2022).


Figure 4: Structure of Methane
Source: Britannica,(2022)

According to experimental studies, it was shown that subjects producing methane have higher increase in the levels of their glucose when an oral glucose test was carried out compared to non-methane producing subjects but there was no outstanding difference in the insulin resistance of subjects producing methane (Mathur*et al*.,2014).This suggest that subjects with increase levels of methane in the intestine may also have impaired glucose tolerance increase when affected with a high carbohydrate load, and may have high tendency of developing hyperglycemia.(Mathur*et al*.,2014).

**Diabetes Mellitus and Other Occupational Chemicals:** Other widely used industrially chemicals include Polychlorinated Biphenyls (PCBs), Tetrachlorodibenzo-p-dioxin (TCDD), Triclosan, etc.

**Polychlorinated Biphenyls(PCBs):** Oneof the man-made organic chemicals that contain carbon, hydrogen and chlorine atoms is the polychlorinated Biphenyls( figure 5). Dielectric and coolant fluids in electrical equipment are polychlorinated biphenyls. In a study conducted on pregnantwomen who were diabetic (primarily type 1), Increase in the serum levels PCBs were linked with diabetes(Longnecker*et al*., 2001). Another epidemiological study, however, showed

inverse link between an increased PCB-135 or p.p`DDE serum level during pregnancy and development of Type 1 diabetes mellitus in the child, but this was not statistically significant (Rignell-Hydbom *et al*., 2010). Studies carried out revealed that employees working in factories were PCB are producedhad higher anti-glutamic acid decarboxylase (anti-GAD) antibodies prevalence in their serum compared to controls, supporting the polychlorinated biphenylseffects on autoimmunity (Langer *et al*.,2002).

In studies conducted on animals exposed to persistent organic pollutants, an increase in insulin resistance was seen, indicating T2DM development (Ibrahim *etal*.,2011)and the link between serum PCB levels and T2DM in humans have been shown by numerous studies (Carpenter *et al.,*2006). Dioxins and dioxin like PCBs act via the aryl hydrocarbon receptor (AhR) and can cause Oxidative stress, apoptosis, and increased inflammation can be caused by dioxins and dioxin like PCBs which act via the aryl hydrocarbon receptor, during metabolization/detoxification of the chemical ( Everett *et al*.,2011).

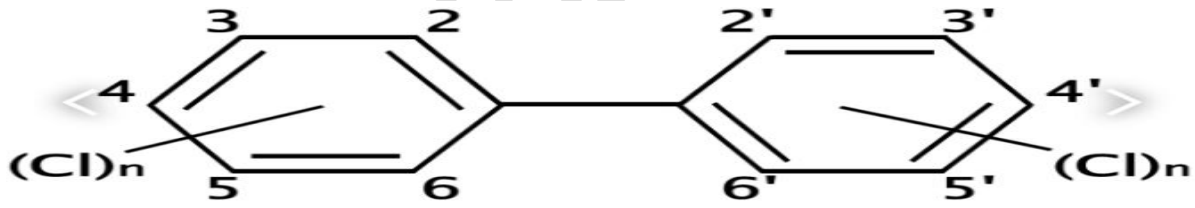


Figure 5: Structure of Polychlorinated Biphenyls
Source: Longneck*er et al.*,(2021)

**7,8-Tetrachlorodibenzo-pdioxin(TCDD):**7,8Tetrachlorodibenzo-p-dioxin (TCDD) is a chemical with a chemical formula $C_{12}H_4Cl_4O_2$ (figure 6) and it is a byproduct formed during the manufacture of materials that require the use of chlorinated and during the combustion of chlorinated chemical products. It has been used in widely in herbicide production (Holsapple*et al.*, 1991). Exposure of humans to this chemical is mainly through Intake of marine food and

result in the exposure of humans to this chemical, due to accumulation of the chemical in fatty tissue in the food chain.

Toxicity to insulin-secretingcells (INS-1E) of rat pancreatic beta cells, despitesurvival and ultrastructure via activation of the aryl hydrocarbon receptor was seen in a study carried out(Martino *et al*., 2013). Also, many experimental studies have shown an impairment in glucose-stimulated secretion of insulin from the islets via the AhR signaling pathway in mice exposed to TCDD(Kurita *et al*.,2009). TCDD exert adverse effects on beta cells by stimulating continuous insulin release resulting in beta cell exhaustion in an INS-1 rat beta-cell line (Kim *et al.,* 2009).

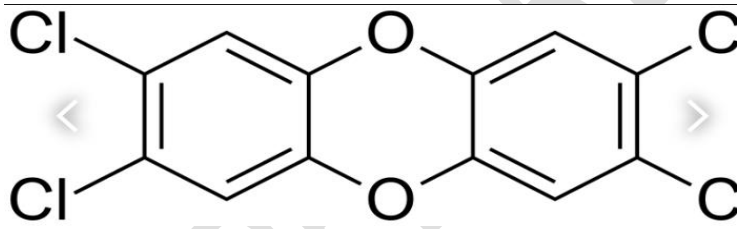


Figure 6: Structure of 7,8-Tetrachlorodibenzo-p-dioxin (TCDD)
Source: Holsapple *et al.*,(1991)



**PolybrominatedDiphenyl Ethers:** Polybrominateddiphenyl ethers (PDBE) are chemicals used as retardants of flames in building materials, textiles, furnishings, and electronics. Ingestion of food and inhalation of air contaminated with polybrominateddiphenyl ethers results in exposure of humans to this chemicals. Studies carried out on mice shown hyperglycemiainduction, decreased insulin, increased glutathioneand superoxide dismutase

levels in the serum and increased TNFα levels in the serum on exposure of mice to the chemical, probably via oxidative induction ( Zhang *et al*.,2013).

**Perfluorinatedakyl Substance:** Perfluorinatedalkyl substances (PFAS) are substances having attractive lipid and water repelling properties, used as fire extinguishing foam, textiles, kitchen ware, and food packaging materials. Human are exposed to PFAS primarily through diet via marine food and game. Epidemiological study reported that increased serum level of the perfluorononanoic acid (PFNA) in human adolescents is associated with decreased blood insulin and beta-cell function (Lin *etal*., 2009). In elderly population, increase PFAS level in the serum is linked with diabetes and studies shown that PFAS can alter glucose metabolism in humans and induce T2DM ( Kind *et al*., 2014).

**Management Approach to Chemical Exposure**

Some of the management approach to reduce the effects of occupational chemicals on diabetic include:

- Use of protective cover such as gloves, masks, etc. to reduce contact with the chemicals
- Washing of hands with soap and warm water after using the chemicals
- Keep the work area ventilated
- Read the instructions for how to use the chemical properly

**SUMMARY**

In this research work, it was interesting to know that some occupational chemicals can increase the risk of diabetes mellitus. In a study carried out on pregnant women with diabetes (primarily type 1), Polychlorinated Biphenyl serum levels were linked with Type 1 diabetes mellitus.

Exposure to cadmium which is an heavy metal shows an escalation in glucose and serum concentration decrease in experimental animals compared to control animals. Hyperglycemia, decreased insulin, increased glutathione, and superoxide dismutase levels in the serum, increasedTNFα levels in the serum, through the induction of oxidative damage was seen in experimental mice exposed to polybrominateddiphenyl.

## CONCLUSION

Some occupational have been seen to have adverse effects on diabetes mellitus. These occupational chemicals could be metals, hydrocarbons or other compounds. These chemicals exert their effects via different mechanisms.

## REFERENCE


Afusco, D., Stazi, M.A., Cotichini, R. and Mazzea, M. (2002).Permanent diabetes mellitus in the first year of life, Dialectologies. 46(1):798–804.

Atkinson, M.A., Eisenbarth, G.S. and Michaels, A.W. (2014).Type 1 diabetes. Lancet, 383(9911): 69–82.

Argos, M., Parvez, F., Rahman, M., Rakibuz-Zaman, M., Ahmed, A., Hore, S.K., Islam, T., Chen, Y., Pierce, B.L., Slavkovich, V., Olopade, C., Yunus, M., Baron, J.A., Graziano, J.H.andAhsan, H.(2014). Arsenic and lung disease mortality in Bangladeshi adults. Epidemiology, 25(4): 536-543.

Bahadar, H., Mostafalous, S. and Abdollahi, M. (2014) Current effects of benzene: A global concern. Toxicology and understandings and perspectives on cancer health. Applied Pharmacology, 276(2): 83-94.

Barroso, I., Gurnel, M., Crowley, V.E,.Agostini, M., Schwabe, J.W. and Soos, M.A. (1999).Domnant negative mutations in human PPARgamma associated with severe insulin resistance, diabetes melitus and hypertension., Nature, 402 (6764): 880–883

Bartoli, D., Battista, G. and DeSantis, M. (1998). Cohort study of art glassworkers in Tuscany, Italy: Mortality from non-malignant diseases. Occupational Medicine (London), 48(7): 441-445.

Barros, S. P., Wirojchanasak, S., Barrow, D. A., Panagakos, F. S., Devizio, W. and Offenbacher, S. (2010).Triclosan inhibition of acute and chronic inflammatory gene pathways.Journal of Clinical Periodontology. 37(5):412–418.

Beard, J., Sladden, T. and Morgan, G. (2003) Health impacts of pesticides exposure in cohort of outdoor workers. Environmental Health Perspectives, 111(5):724-730.

Bener, A., Obineche, E. and Gillette, M. (2001) Association between blood levels of lead, blood pressure and risk of diabetes and heart disease in workers. International Archive of Occupational and Environmental Health, 74(5):375-378.

Bertelsen, R. J., Longnecker, M. P. and Løvik, M.(2013). Triclosan exposure and allergic sensitization in Norwegian children. Allergy, 68(1): 84–91.

Bodin J., Bolling, A. K., Samuelsen, M.., Becher, R.., Lovik, M.andNygaard, U.C. (2013).Long-term bisphenol exposure accelerates insulitis development in diabetes-prone NOD mice. Immunopharmacology and Immunotoxicology, 35(3):349–358.

Bond, G., McLaren, E. and Baldwin, C. (1986). An update of mortality among chemical workers exposed to benzene. British Journal of Industrial Medicine, 43(10):685-691

Britannica.(2022).The Editors of Encyclopaedia. "methane". Encyclopedia Britannica. Carpenter, D. O.(2006). Polychlorinated biphenyls (PCBs): Routes of exposure and effects on human health. Reviews on Environmental Health. 21(1):1–23.

Center for Disease Control (2008).Environmental contaminants as risk factors for developing diabetes. Reviews on Environmental Health, 23(1): 59–74.

Centers for Disease Control and Prevention.(2014). National diabetes statistics report: Estimates of Diabetes and its burden in the United States, Atlanta: U.S. Department of Heath and Human Services.

Chen, Y. W., Yang, C. Y, Huang, C. F., Hung, D. Z., Leung, Y. M. and Liu, S. H. (2009). Heavy metals, islet function and diabetes development. Islets,1(3):169–176.

Dangleben, N. L., Skibola, C. F. and Smith, M. T. (2013). Arsenic immunotoxicity: A review. Environmental Health,12(1):73-75.

Dobson, L, Sheldon, C. D. and Hattersey, A. T. (2004). Understanding cystic fibrosis-related dabetes: Best thought of as insulin deficiency. Journal of the Royal Society of Medicine, 97 (44):26–35.

Douillet, C., Currier, J., Saunders, J., Bodnar, W. M., Matoušek, T.andStýblo, M. (2013). Methylated trivalent arsenicals are potent inhibitors of glucose stimulated insulin

secretion by murine pancreatic islets. Toxicology and Applied Pharmacology, 267(1):11–15.

Donohue, K. M., Miller, R. L.andPerzanowski, M. S.(2013).Prenatal and postnatal bisphenol A exposure and asthma development among inner-city children. Journal of Allergy and Clinical Immunology, 131(3):736–742.

EiSenbarth, G. S. (2007). Update in type 1 diabetes. Journal of Clinical Endocrinology and Metabolism, 92(7): 2403–2407.

Esposti, M. D., Ngo, A., Myers, M..A. (1996).Inhibtion of mitochondracomplex may account for IDDM induced By intoxication with the rodenticide Vacor. Diabetologies. 45(11):1531–1534

Everett, C. J., Frithsen, I. and Player, M. (2011). Relationship of polychlorinated biphenyls with type 2 diabetes and hypertension. Journal of Environmental Monitoring, 13(2):241–251.

Ewald, N., Kaufmann, C., Raspe, A., Kloer, H.U., Bretze, R.G. and Hardt, P.D. (2012). Prevalence of diabetes mellitus secondary to pancreatic diseases (type 3c).Diabetes Metabolismn. Research Review, 28(4):338–342.

Fabris, P., Betterle, C., Greggio, N.A., Zanchetta, R., Bosi, E.andBiasin, M. R. (1998). Insulin dependent diabetes mellitus during alpha interferon therapy for chronic vralhepatits. Journal of Hepatology, 8(3):514–517.

Ferguson, J. E. (1990). The heavy elements: Chemistry, environ-mental impact and health effects. Oxford, NY: Pergamon Press; P. 211–2.36.

Forrest, J.M., Menser, M. A. and Burgess, J.A. (1971).High frequency of diabetes mellitus in young adults with congenital rubella. Lancet, 298(7720): 332-334.

Fraga, C. G. (2005). Relevance, essentiality and toxicity of trace elements in human health. Molecular Aspectsof Medicine, 26(4-5):235–44.

Gerd, C., Hartmut, H., Helmut, G.(2003). Naphthalene and Hydronaphthalenes.Ullmann's Encyclopedia of Industrial Chemistry. Global Diabetes community (2019).Causes of Diabetes, p.22-34.

Global report on diabetes Geneva: Word Health Organization (2016). P.66

Grivetti, L. E and Ogle, B. M. (2000).Value of traditional foods in meeting macro-and micronutrient needs: The wild plant connection. Nutritional Research Review, 13(1):31–46.

Han, J.C, Park, S.Y., Hah, B. G., Choi, G. H., Kim, Y. K, Kwon, T. H., Kim, E. K, Lachaal, M., Jung, C.Y., and Lee, W. (2003). Cadmium induces impaired glucose tolerance in rat by

down-regulating GLUT4 expression in adipocytes. Archives of Biochemistry and Biophysics, 413(2):213–215.

Hattersley, A., Bruining, J., Shied, J., Njolstad, P.andDonaghue, K.C. (2009). The diagnosis and management of monogenic diabetes in children and adolescents. Pediatric Diabetes, 10(12):33–42.

Hattersley, A., Bruning, J., Shed, J., Njolstad, P.andDonaghue, K. S.(2006). Clinical practice consensus guidelines 2006-2007.The dagnosis and management of monogenic diabetes n children.Pediatric Diabetes. 7(1):352-360

Hattersley, A.T. and Pearson, E.R. (2006). Mini review: Pharmacogenetics and beyond: The interaction of therapeutic response, beta-cell physiology, and genetics in diabetes. Endocrinology, 147(6): 2657-2663.

Hartoft-Nielsen, M. L., Rasmussen, A.K., Bock, T., Feldt-Rasmussen, U., Kaas, A., and Buschard K.(2009). Iodine and tri-iodo-thyronine reduce the incidence of type 1 diabetes mellitus in the autoimmune prone BB rats. Autoimmunity, 42(2) 131–138.

Hectors, T.L., Vanparys, C. and Vander-ven K. (2011). Environmental pollutants and type 2 diabetes: A review of mechanisms that can disrupt beta cell function. Diabetologia, 54(6): 1273–1290.

Holsapple, M. P., Snyder, N. K., Wood, S. C.and Morris, D. L. (1991). A review of 2,3,7,8-tetrachlorodibenzo-p-dioxin-induced changes in immunocompetence. Toxicology. 69(3):219–255.

Hirata, Y., Ishzu, H. (1972). Elevated insulin binding capacity of serum proteins in a case with spontaneous hypoglycemia and mild diabetes not treated with insulin. Journal of Experimental Medicine, 107(1):277–286 .

Hu, F. B (2011) Globalization of diabetes: The role of diet lifestyle, and genes. Diabetes Care, 34(6): 1249–1257.

Ibrahim, M. M., Fjære, E.and Lock, E. J.(2011). Chronic consumption of farmed salmon containing persistent organic pollutants causes insulin resistance and obesity in mice. PLoS ONE. 6(9): 2517-2518.

Internatonal Diabetes Federation (IDF).Dabetes Atlas 8th Edition. Brusses: 2017.p.143-156.International labour organization (ILO,2015) Hydrocarbons, halogenated aromatic. P.567.

Jackson, W., Hofman, P.L., Robinson, E.M., Eliot, R.B., Pilcher, C. C.andCutfied, W. S. (2001). The changing presentation of children with newly diagnosed type 1 diabetes melitus. Pediatric .Diabetes, 2(4):154- 159

Jörg, F., Ulric,h G. and, Simo, T. A. (2005). Toluene.Ullmann's Encyclopedia of Industrial Chemistry.p.74

Kara, R.(2017). Encyclopedia Britannica. Diabetes mellitus; medical disorder.p.34-35

Kahn, S. E., Cooper, M. E. and De-Prato S. (2014). Pathophysiology and treatment of type 2 diabetes: Perspectives on the past, present, and future. Lancet, 38(3):1068-1083.

Kahn, C. R., Baird, K., Fiier, J. S. and Jarrett, D. B. (1997).Effects of auto-antibodies to the insulin receptor on isolated adipocytes.Studies of insulin binding and insulin action. Journal of Clinical Investigation, 60(1):1094-1106.

Kahn, S. E., Cooper, M. E. and De-Prato S. (2014). Pathophysiology and treatment of type 2 diabetes: Perspectives on the past, present, and future. Lancet, 38(3):1068-1083.

Kahn, C.R., Flier, J.S., Bar, R.S., Archer, J.A., Gorden, P.and Martin, M.M.(1976). The syndromes of insulin resistance and acanthosisnigricans. Insuin-receptor dsorders in man. New England Journal of Medicine, 29(4):739–745

Kajta, M., Litwa, E. and Rzemieniec, J.(2014). Isomer-nonspecific action of dichlorodiphenyltrichloroethane on aryl hydrocarbon receptor and G-protein-coupled receptor 30 intracellular signaling in apoptotic neuronal cells. Molecular and Cellular Endocrinology, 392(12): 90–105.

Kerkvliet, N. I., Steppan, L. B.andVorachek, W., (2009). Activation of aryl hydrocarbon receptor by TCDD prevents diabetes in NOD mice and increases Foxp3+ T cells in pancreatic lymph nodes. Immunotherapy, 1(4):539–547.

Khan, A.R. and Awan, F.R. (2014). Metals in the pathogenesis of type 2 diabetes. Journal of Diabetes Metabolism Disorder, 13(1):16-18.

Kim, Y. H., Shim, Y. J., Shin, Y. J., Su,l D., Lee, E. and Min, B. H. (2009). 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) induces calcium influx through T-type calcium channel and enhances lysosomal exocytosis and insulin secretion in INS-1 cells. International Journal of Toxicology, 28(3):151–161.

King, M.L., Shaikh, A., Bidwel, D., Voler, A.andBanatvaa, J.E. (1983). Coxsackie Bv specific IgM responses in Children with insulin dependent (juvenile onset; type I) diabetes mellitus Lancet,1(2):1397–1399.

Kurita, H., Yoshioka, W., Nishimura, N., Kubota, N., Kadowaki, T.andTohyama, C. (2009). Aryl hydrocarbon receptor-mediated effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on glucose-stimulated insulin secretion in mice. Journal of Applied Toxicology, 29(8):689–694.

Langer, P., Tajtákova, M.andGuretzki, H. J., (2002)..High prevalence of anti-glutamic acid decarboxylase (anti-GAD) antibodies in employees at a polychlorinated biphenyl production factory. Archives of Environmental Health. 57(5):412–415

Lei, L., Jin, T., Zhou, Y., Zhonghua, L.D., Wei, S. Z. and Ye, B. Z.(2006). The effects of cadmium on the levels of insulin in smelters. Lancets, 24(1):3–6.

Leso, V., Ricciardi, W., Lops, E. A.andLavieoli, I. (2017). Occupational chemical exposure and diabetes mellitus risk. Article in Toxicology and Industrial Health, 74(5):375-378.

Li, J., and McMurray, R. W. (2009).Effects of chronic exposure to DDT and TCDD on disease activity in murine systemic lupus erythematosus.Lupus. 18(11):941–949.

Lin, C. Y., Chen, P. C., Lin, Y. C. and Lin, L.Y. (2009).Association among serum perfluoroalkyl chemicals, glucose homeostasis, and metabolic syndrome in adolescents and adults. Diabetes Care, 32(4):702–707.

Lind, L., Zethelius, B., Salihovic, S., Bavel, B. and Lind, P. M. (2014).Circulating levels of perfluoroalkyl substances and prevalent diabetes in the elderly.Diabetologia, 57(3):473–479.

Longnecker, M..P.,, Klebanoff, M.A., Brock, J.W. and Zhou, H.(2001). Polychlorinated biphenyl serum levels in pregnant subjects with diabetes. Diabetes Care, 24(6):1099–1101.

MacFarlane, I. A. (1997).Endocrine dsease and diabetes melitus. In: Textbook of diabetes. 2nd ed. Pickup J.C, Wiliams G, Eds. Oxford Blackwel.P.64.1064.

Madsbad, S., Krarup, T., Regeur, L., Faber, O. K. and Binder, C. (1980). Insulin secretory reserve in insulin dependent patients at time of diagnosis and the first 180 days of insulin treatment. Endocrinology, 95(2):359–363.

Mathur, R., Goyal, D., Kim, G., Barlow, G. M., Chua K.S and Pimentel, M. (2014). Methane-producing human subjects have higher serum glucose levels during oral glucose challenge than non-methane producers: A Pilot study of the effects of enteric methanogens on glycemic regulation. Research Journal of Endocrinology and Metabolism,6(3): 2053-3640.

Martino, L., Masini, M.andNovelli, M., (2013). The aryl receptor inhibitor epigallocatechin-3-gallate protects INS-1E beta-cell line against acute dioxin toxicity. Chemosphere. 93(8):1447–1455.

Mauvais, J. F., Sobngwi, E., Porcher, R., Rivelne, J.P., Kevorkian, J.P. and Vaisse, C.(2004). Ketosis prone type 2 diabetes in patents of Sub-Saharan African origin.Clinical pathophysiology and natural history of B-Cell dysfunction and insulin resistance.Diabetes. 53(4):645–653

Merory, J. (1968). Food Flavorings: Composition, manufacture and use (2nded.). Westport, CT: AVI Publishing Company, Inc.p.43.

Mooy, J.M., Grootenhuis, P.A., de-Vries, H., Valkenburg, H.A., Bouter, L.M.andKostense, P.J.(1995). Prevaence and determinants of glucose intolerance in a Dutch caucasan population.The Hoorn Study. Diabetes Care, 18(1):1270–1273.

Owen, K.R., Groves, C., Hanson, R.L., Knower, W.C., Shuldiner, A.R. and Ebein, S.C. (2007). Common variation in the LMNA gene (encoding lamin A/C) and type 2 diabetes: Association analyses in 9,518 subjects. Diabetes, 56(3): 879-883.

Pandit, M.K., Burke, J., Gustafson, A.B., Minocha, A. and Peris, A.N.(1993). Drug induced disorders of glucose tolerance. Annal International Journal of Medicine, 118(7):529–539.

Patterson, C.C., Dahlquist, G.G., Gyürüs, E., Green, A.andSoltesz, G.(2009). Incidence trends for childhood type 1 diabetes in Europe during 1989–2003 and predicted new cases 2005–20: A multicentre prospective registration study. Lancet, 373(9680):2027–2033.

Pearson, E.R., Boj, S.F., Steee, A.M., Barrett, T., Stals, K.and Shield, J.P.,(2007).Macrosomia and hyperinsulinaemic hypoglycemia in patients with heterozygous mutations in the HNF4A gene. PLoS.Med, 4(1):118-119.

PerL, S., Kushner, J.A., Buchholz, B.A., Meeker, A.K., Stein, G.M. and Hsieh, M. (2010). Significant human β Cell turnover is limited to the first three decades of life as determined by in vivo thymidneanaog incorporation and radiocarbon dating. Journal of Clinical .Endocrinology and Metabolism, 95(1): 234–239.

Permert, J., Larsson, J., Westermark, G.T., Herrington, M.K., Christmanson, L. and Pour, P.M.(1994). Set amyoid polypeptide in patients with pancreatic cancer and diabetes. New England Journal of Medicine, 330(7):313–318

Fact Sheet" (PDF).Archive.epa.gov. U.S. Environmental Protection Agency.P.67-89.

Rager, J. E., Bailey, K. A. and Smeester, L.(2014). Prenatal arsenic exposure and the epigenome: Altered microRNAs associated with innate and adaptive immune signaling in newborn cord blood. Environmental and Molecular Mutagenesis. 55(3):196–208.

Rignell-Hydbom, A., Elfving, M. and Ivarsson, S. A.(2010). A nested case-control study of intrauterine exposure to persistent organochlorine pollutants in relation to risk of Type 1 diabetes. PLoS ONE, 5(6) 1128-1129.

Rosensten, E.D., Advani, S., Reitz, R.E. and Kramer, N.(2001). The prevaence of insuln receptor antibodies in patients with systemic lupus erythematosus and related conditions. Journal of Clinical Rheumatology, 7(1):371–373.

Schmid, J.V. and Bradfield, C. A.(1996). AH receptor signaling pathways. Annual Review of Cell and Developmental Biology, 12(34): 55–89.

Shields, B.M., Hicks, S., Shepherd, M.H., Colclough, K., Hattersley, A.T. and Elard, S.(2010). Maturity-onset diabetes of the young (MODY): How many cases are we missing? Dialectologies. 53(12):2504-2508.

Shinomiya, M., Nadano, S., Shinomiya, H. and Onji, M.(2002). In situation characterization of dendritic cells occurring in the islets of non-obese diabetic mice during the development of insulitis. Pancrease. 20(3):290–296.

Singh, P. (2017). Over 73% of paints found to have excessive lead: Study. Times of India.P.55.

Silderberg, M. (2004). Hydrocarbons.in: Chemistry: The molecular nature of matter and change. New York:McGraw-HillCompanies, p. 620-631.

Sobngwi, E. and Gautier, J.F.(2002). Adult-onset idiopathic Type I or ketosis-prone type I diabetes: Evidence to revisit diabetes classification. Dialectologies.;45(5):283-285.

Soetan, K.O., Olaiya, C. O. and Oyewole, O. E. (2010). The importance of mineral elements for humans, domestic animals and plants: A review. African Journal of Food Science. 4(5):200–222.

Sorgjerd, E.P., Skorpen, F., Kvaloy, K., Midthjel, K. and Gril, V.(2012). Time dynamics of autoantibodies are coupled to phenotypes and add to the heterogeneity of autoimmune diabetes in adults: The HUNT study, Norway. Dialectologies. 55(7):1310–1851.

Soriano, S., Alonso-Magdalena, P. and García-Arévalo, M.(2012). Rapid insulinotropic action of low doses of bisphenol-A on mouse and human islets of Langerhans: Role of estrogen receptor β. PLoS ONE. 7(2): 31108- 31109.

Stumvol, M., Godstein, B. J. and van Haeften, T.W.(2005). Type 2 diabetes: Principles of pathogenesis and therapy. Lancet, 365(9467):1333-1346.

Sylvester, G. S., Esiet, U. I. and Ajibola, D. O. (2015).Effect of Gongronemalatifolium leaf extract on blood biochemical Assay in Diabetic Rats. Diabetologies,67(2):32-35.

Tattersal, R.B.(1974). Mild familial diabetes with dominant inheritance. Quarterly Journal of Medicine 43(76):339–357.

Taylor, S. and Ariogu, E.(1999). Genetically defined forms of diabetes in children. Journal of Clinical Endocrinoogy and Metabolism, 84(12):4390–4396.

Taylor, S.I. and Lily, L.(1992). Molecular mechanisms of insulin resistance.Lessons from patients with mutations in the insulin-receptor gene.Diabetes. 41(12):1473-1490.

Tuomi, T., Groop, L, Zimmet, P., Rowley, M. and Mackay, E.(1993). Antibodies t o glutamic acid decarboxylase (GAD) reveal latent autoimmune diabetes mellitus in adults with a non-insulin dependent onset of disease. Diabetes. 42(5):359-362.

Tuomi, T., Santoro, N., Caprio, S., Cai, M., Weng, J. and Groop, L.(2014). The many faces of diabetes: A disease with increasing heterogeneity. Lancet, 383(9922):1084-1094.

Vandenberg, L. N., Chahoud, I., Heindel, J. J., Padmanabhan, V., Paumgartten, F. J. R. and Schoenfelder, G.(2010). Urinary, circulating, and tissue biomonitoring studies indicate widespread exposure to bisphenol A. Environmental Health Perspectives, 118(8):1055–1070.

Wesley, T.A., Nalinie, S. W., Srinivas, D.S., Daniel, J. C., Aruni, B., Sanjay, S. and Timothy, E. O. (2019). Benzene Exposure Induces Insulin Resistance in Mice. Toxicological Sciences, 167(2):426–437.

World Health Organization (WHO,2019). Classification of diabetes mellitus. P.234-256.World Health Organization (WHO,2017). Percentage prevalence of diabetes mellitus P.134-156.

Winter, W.E., Macaren, N.K., Riey, W.J., Clarke, D.W., Kappy, M.S. and Spilar, R.P. Maturity-onset diabetes of youth in black Americans. New England Journal of Medicine. 316(5):285–291.

Yajnik, C. S., Shelgikar, K.M., Naik, S.S., Kanitkar, S.V., Orskov, H. and Alberti K.G.(1992). The ketosis-resistance in Fibro-calculous-pancreatic-dabetes. Clinical observations and endocrine-metaboic measurements during oral glucose tolerance test. Diabetes Research Clinical Practice, 15(2):149-156.

YoshimasaK.,Osamu, K., Takuya, D., Takeshi, K., Hiratsuka, H., Tsuchitani, M. and Umemura, T.(2003). Chronic cadmium treatment induces islet B-cell injury in ovariectomizedcyanomolgus monkeys. Japan Journal of Veterinary Research, 50(4):175-83.

Zhang, Z., Sun, Z. Z. and Xiao, X.(2013). Mechanism of BDE209-induced impaired glucose homeostasis based on gene microarray analysis of adult rat liver. Archives of Toxicology. 87(8):1557–1567.

Zimmet, P., Aberti, K.G. and Shaw, J.(2001). Global and societal implications of the diabetes epdemic. Nature, 414(86):782–787.